Immunology

Anaphylaxis as an adverse event following immunisation

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A review of the definitions of anaphylaxis and discussion of the challenges for vaccine safety

Anaphylaxis is an acute hypersensitivity reaction with multi-organ system involvement that can rapidly progress to a severe life-threatening reaction. It has been difficult to provide a robust clinical definition of anaphylaxis because of the non-specificity of symptoms and variability of presentation. Anaphylaxis can occur to a variety of allergens, and is a rare, but well recognised adverse event following immunisation (AEFI). Several groups have recently tried to provide a working definition of anaphylaxis. This editorial reviews these definitions and discusses the challenges for vaccine safety in reliably identifying anaphylaxis as an AEFI.

Anaphylaxis may occur following exposure to allergens from a variety of sources including food, aeroallergens, venom, drugs, and immunisations. Vaccines are a mixture of compounds and allergic sensitisation can occur to any component. Individuals may be sensitised to the vaccine antigens, adjuvants (e.g., alum), excipients used in the manufacturing process (e.g., gelatin, neomycin) or a latex stopper on the vial.[1 2]

Anaphylaxis as an AEFI is a concern to many health care professionals involved in the administration of immunisation programmes. An example of the level of concern can be seen by the large number of children with egg allergy referred for measles, mumps and rubella (MMR) immunisation in hospital, based on concerns about anaphylaxis. Children who have had an allergic reaction to egg, but not anaphylaxis, can be immunised without any special precautions. However, anaphylaxis is a well recognised AEFI, which may in principle occur following any immunisation without prior warning.[1] The potential for vaccines to cause anaphylaxis has two important consequences. Firstly, immunisers must be able to recognise and treat anaphylaxis in the clinic setting. Secondly, immunisation programmes must be able to reliably identify cases and to examine the potential causal relationship of the event to immunisation. The management of anaphylaxis is discussed elsewhere.[3 4] This editorial discusses the challenges of reliably identifying anaphylaxis as an AEFI for vaccine safety programmes.

INCIDENCE

Anaphylaxis following immunisation is a rare event. Even the largest pre-licensure vaccine trials are unlikely to detect a single case, let alone provide an estimate of incidence. The onus for detection of anaphylaxis falls to national post-marketing surveillance systems. The ''yellow card'' reporting system of the Medicines and Healthcare products Regulatory Agency in the UK (www.mhra.gov.uk) received 130 reports of anaphylaxis associated with immunisation in the six years from 1997 to 2003, suggesting a rate of 1 per million doses.[5] Likewise, the US Vaccine Adverse Event Reporting System (http://vaers.hhs.gov) recorded 452 reports of ''anaphylactoid reactions'' in over 1.9 billion doses of vaccine administered countrywide over a 10-year period.[6] This yields an estimated incidence of 0.2 cases per million doses. All post-marketing surveillance systems rely on passive reporting of cases and are prone to underreporting. Also these incidences are of overall rates of reaction and do not reflect incidences following individual vaccines.

There are a limited number of studies specifically addressing the incidence of anaphylaxis as an AEFI. Patja *et al* describe 30 cases of anaphylaxis occurring after MMR vaccination over a 14-year period, deriving an incidence estimate of 1 per 100 000.[7] In a retrospective analysis of hospital discharge records, Bohlke *et al* identified five cases of anaphylaxis in 7.5 million doses of vaccine, giving an incidence rate of 0.65 cases per million doses.[8] Yet in two of these five ''cases'', uncertainties remained about the true nature of these events. The retrospective design of this study made it impossible to clarify these further. As with most advanced immunisation programmes, children received combination vaccines with multiple immunisations at a single clinic visit, making it impossible to attribute risk to a single vaccine or component. These studies exemplify the difficulty of describing anaphylaxis as an AEFI in any detail using retrospective analyses.

CLINICAL SYMPTOMS

Anaphylaxis is a clinical syndrome characterised by its sudden onset, rapid progression and the involvement of multiple organ systems. At its most severe, the cardiovascular and respiratory system are involved with shock, bronchoconstriction and laryngeal oedema.[4 9] Erythema, itching and urticaria are common features and there may be angioedema of subcutaneous tissue. The gastrointestinal tract may become involved, with non-specific symptoms such as incontinence, vomiting, abdominal pain and diarrhoea. The central nervous system can be affected, including a feeling of impending doom and unconsciousness (probably related directly to hypotension and hypoxia). Biomarkers, such as the measurement of serum mast cell tryptase, have been used to identify cases, but are neither sensitive nor specific enough to make the diagnosis.[10] The differential diagnosis of anaphylaxis includes syncope, panic attack, hypotonic-hyporesponsive episode, myocardial infarction, acute asthma and hereditary angioedema. All of these conditions have overlapping non-specific symptoms that are difficult to differentiate from anaphylaxis.

To add to the complexity of identifying cases, there is considerable variability in the clinical presentation of anaphylaxis. On the one hand, the course of the reaction may be so rapid that there is only partial clinical expression before death ensues.[11] On the other hand, prompt treatment may abort an evolving anaphylactic reaction, also leading to partial expression of symptoms. Grading symptom severity may be a useful way of recognising such partially expressed reactions.[4 9] The Mueller grading system (table 1) is the most well known of these, and was first published in the context of insect venom allergy.[12] Anaphylaxis from envenomation may be a good model for vaccine related anaphylaxis because of the similarities in delivery of allergen by parenteral subcutaneous or intramuscular injection. However, the grading is used to define severity of anaphylaxis rather than being a case definition of anaphylaxis in its own right.

Thus the variability and partial expression of clinical anaphylaxis create a challenge for the development of a case definition. Until recently there has been no standard. In the absence of a diagnostic

Table 1 Mueller's grading for systemic allergic reactions[12]

I	Generalised urticaria, periorbital oedema, itching, malaise, anxiety
II	Angioedema or two or more of the following: chest or throat tightness, nausea, vomiting, diarrhoea, abdominal pain, dizziness
III	Dyspnoea, wheezing, or stridor, or two or more of the following: dysphagia, dysarthria, hoarseness, weakness, confusion, feeling of impending disaster
IV	Hypotension, collapse, loss of consciousness, incontinence, cyanosis

test we must rely on clinical symptoms alone to make a diagnosis.

ESTABLISHING A CASE DEFINITION

To date, studies reporting anaphylaxis as an AEFI have used various definitions as opposed to external standards. This makes comparison of their results more difficult and prone to misinterpretation. However, three definitions have recently been devised and these should provide a benchmark for future studies of vaccine safety.

THE EUROPEAN ACADEMY OF ALLERGOLOGY AND CLINICAL IMMUNOLOGY (EAACI)

EAACI defines anaphylaxis as a ''severe, life-threatening, generalised or systemic hypersensitivity reaction'', a definition later adopted by the World Allergy Organization.[13 14] The definition emphasised the gradual onset and progression of symptoms from itching in the gums or throat through to a multi-organ reaction ''dominated by severe asthma'' with ensuing hypotension. However, hypotension and bronchospasm did not have to be present to class the reaction as anaphylaxis. This would permit reactions that were aborted at an early stage, by administration of epinephrine, to be classed as anaphylaxis, and because of this EAACI provides a useful definition for the clinic setting.

THE SECOND SYMPOSIUM ON THE DEFINITION AND MANAGEMENT OF ANAPHYLAXIS

The findings of the Second Symposium on the definition and management of anaphylaxis were published recently.[15] This global expert symposium agreed a clear and concise definition of anaphylaxis as a ''serious allergic reaction that is rapid in onset and may cause death''. However, while this stresses the importance of anaphylaxis, most cases are not fatal and will not be included by a definition that expresses only a potential for harm.

The diagnostic criteria for the case definition were also less than clear in their ability to capture cases of anaphylaxis as an AEFI. There were three possible pathways to reach a diagnosis. Two pathways were linked to known or likely allergens for that patient—and are therefore not suitable for a vaccine related definition, as we shall discuss later. The other pathway relies on the presence of skin symptoms as an essential element of its diagnostic criteria. This may not be present in reactions to vaccines, as reactions following episodes of envenomation demonstrate. In one series of cases, where at least 30% were due to insect stings, skin symptoms such as generalised itch and urticaria was present in 55% and erythema in only 73% of cases.[9] In a series of fatal anaphylactic reactions, none of 21 cases that were caused by drugs had developed erythema or cutaneous oedema.[11] Skin symptoms are also less likely to occur in children with the most severe respiratory and cardiovascular symptoms.[16] As such, the Second Symposium definition does not appear to be appropriate for recording anaphylaxis as an AEFI.

ANALYSING THE RELATIONSHIP OF CAUSE AND EFFECT

One important aspect of providing a definition of an adverse event is the need to separate the event from any specific cause. Many vaccine safety studies have used the temporal association of immunisation as part of the case definition of the anaphylaxis event itself.[17] To establish a causal relationship between anaphylaxis and its precipitant, the inclusion of exposure in the case definition of anaphylaxis invokes the *petitio principii*. This is a logical fallacy in which the proposition to be proven is assumed in one of the premises (i.e., circular reasoning). Instead, the outcome (anaphylaxis) should be defined independently from the exposure (allergen), and their relationship examined to establish causality.[18] In anaphylaxis as an AEFI, symptoms occur rapidly after exposure to the allergen. With a time interval of just a few minutes between onset and exposure, there is often little doubt as to the cause of the event.

However, the value of uncoupling the event from its cause can be seen in a theoretical example where anaphylaxis is triggered at a distance from the immunisation procedure itself. A delayed anaphylactic event is theoretically possible as an AEFI to a DNA vaccine, where there would be a window of time for synthesis of the allergen de novo. However other scenarios such as an atypical biphasic reaction, the release of a depot or the delayed metabolism of a vaccine into an allergen, might permit anaphylaxis to occur late after delivery of the vaccine. As we explore novel modes of vaccine delivery we should be aware that such events would only be recognised by vaccine safety studies that did not couple allergen exposure to immediate anaphylaxis.

THE BRIGHTON COLLABORATION

The Brighton Collaboration (www.brightoncolloaboration.org) is establishing globally standardised case definitions for AEFI and guidelines for collection, analysis and presentation of vaccine safety data. This will advance vaccine safety by facilitating comparison of adverse events across trials and surveillance systems. A ''Brighton'' definition of anaphylaxis as an AEFI has just been published.[19] It addresses many of the issues that limit the EAACI and second symposium definitions by specifically considering anaphylaxis as an AEFI. It provides three levels of diagnostic certainty, incorporating the variable completeness of information associated with retrospective data collection. It also does not incorporate exposure to immunisation into the definition, permitting causal analysis to occur independently. However, like all three definitions discussed in this article, it is yet to be validated by use in practice.

CONCLUSIONS

Anaphylaxis is a rare adverse event following immunisation. Designing a case definition for use in epidemiological studies is challenging because of the variety and non-specificity of the symptoms. Despite these difficulties two recent symposia have proposed definitions and the Brighton Collaboration has published a definition to be used specifically for immunisation. We propose that future studies on vaccine safety should use and evaluate this definition as a benchmark for reporting.

Research in this area to date has shown that reliable and well defined incidence rates cannot be derived from passive reporting systems used in post-marketing surveillance. There is a need for large and prospective multinational studies to arrive at a better understanding of the frequency and true nature of this rare event. Only by providing robust data can we expect to reliably assess vaccine safety and maintain public confidence in our immunisation programmes.

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REFERENCES

1 **Madaan A**, Maddox DE. Vaccine allergy: diagnosis and management. *Immunol Allergy Clin North Am* 2003;**23**:555–88.
2 **Pool V**, Braun MM, Kelso JM, *et al*. Prevalence of anti-gelatin IgE antibodies in people with anaphylaxis after measles-mumps rubella vaccine in the United States. *Pediatrics* 2002;**110**:e71.
3 **Brown SG**, Mullins RJ, Gold MS. Anaphylaxis: diagnosis and management. *Med J Aust* 2006;**185**:283–9.
4 **Sampson HA**. Anaphylaxis and emergency treatment. *Pediatrics* 2003;**111**:1601–8.
5 **Department of Health**. Vaccine safety and the management of adverse events following immunisation. *Immunisation against infectious disease*. London: Department of Health, 2006:53–64.
6 **Zhou W**, Pool V, Iskander JK, *et al*. Surveillance for safety after immunization: Vaccine Adverse Event Reporting System (VAERS)—United States, 1991–2001. *MMWR Surveill Summ* 2003;**52**:1–24.
7 **Patja A**, Makinen-Kiljunen S, Davidkin I, *et al*. Allergic reactions to measles-mumps-rubella vaccination. *Pediatrics* 2001;**107**:e27.
8 **Bohlke K**, Davis RL, Marcy SM, *et al*. Risk of anaphylaxis after vaccination of children and adolescents. *Pediatrics* 2003;**112**:815–20.
9 **Brown SG**. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol* 2004;**114**:371–6.
10 **Payne V**, Kam PC. Mast cell tryptase: a review of its physiology and clinical significance. *Anaesthesia* 2004;**59**:695–703.
11 **Pumphrey RS**, Roberts IS. Postmortem findings after fatal anaphylactic reactions. *J Clin Pathol* 2000;**53**:273–6.
12 **Mueller UR**. *Insect sting allergy: clinical picture, diagnosis and treatment*. New York: Gustav Fischer Verlag, 1990.
13 **Johansson SG**, Bieber T, Dahl R, *et al*. Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004;**113**:832–6.
14 **Johansson SG**, Hourihane JO, Bousquet J, *et al*. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001;**56**:813–24.
15 **Sampson HA**, Munoz-Furlong A, Campbell RL, *et al*. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;**117**:391–7.
16 **Braganza SC**, Acworth JP, Mckinnon DR, *et al*. Paediatric emergency department anaphylaxis: different patterns from adults. *Arch Dis Child* 2006;**91**:159–63.
17 **CIOMS**. Definitions and basic requirements for the use of terms for reporting adverse drug reactions (XIII): clinical pathology and general disorders. *Pharmacoepidemiol Drug Saf* 1999;**8**:217–24.
18 **Rothman KJ**. Causation and causal inference. In: Rothman KJ, Greenland S, eds. *Modern epidemiology*. Philadelphia: Lippincott-Raven, 1998:7–28.
19 **Ruggeberg JU**, Gold MS, Bayas JM, *et al*. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine* 2007. Epub ahead of print.

Lymphomania

The urge to classify –
A Pathologist can never defy.
An example of this, in its full splendour
Are the Lymphomas they plunder!

From Rap to Kiel,
From WHO to REAL,
Sifting through clefts and cleaves,
Is a terrifying ordeal.

Sometimes they FISH, sometimes they Rye,
May also end up counting stars in the sky.
In a sea of CDs they sink to the bottom,
Despite this, none can they fathom.

But now, we no longer need fear
For microarrays are here;
To wipe our frowns from across the mile,
And tackle lymphomas with a smile!!

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